Melanocytic naevi with perineurial differentiation a distinctive variant of neurotised naevi and a diagnostic pitfall with desmoplastic melanoma

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Abstract

Aims: Spindle cell differentiation is not an uncommon finding in common acquired naevi and may represent a form of neurotisation with Schwannian differentiation of melanocytes. Perineurial differentiation in this context appears to be distinctly rare and is only poorly documented in the literature.

Methods and results: We have identified six melanocytic tumours showing spindle cell morphology and perineurial differentiation from routine and referral material. Clinical data and follow-up were obtained, and the histological and immunohistochemical features were analysed. The tumours affected middle aged adults (median: 48; range: 26-74 years) with a wide anatomical distribution and benign follow up (median: 13; range: 6 to 48 months). All tumours were nodular and circumscribed but asymmetrical with extension into deep dermis and superficial subcutis. A characteristic finding was a biphasic growth pattern with a lentiginous compound naevus in the superficial aspect and abrupt transition to a prominent nodular spindle cell proliferation in the deeper reaches. Spindle cells were bland and uniform and arranged singly and in short fascicles in a loose fibromyxoid stroma. In areas, a

whorled arrangement of slender spindle cells with wavy nuclei was appreciated. Distinctive intratumoral hypocellular nodules and peripheral lymphoid aggregates were additional features. By immunohistochemistry, the spindle cells were mainly S100-positive melanocytes. In areas, S100-/EMA+ spindle cells showing co-expression of glut-1 and claudin-1 were closely admixed.

Conclusion: This perineurial differentiation likely represents a rare and unusual form of neurotisation. The tumours are benign but may be mistaken for desmoplastic melanoma. Awareness and careful attention to the clinico-pathological and immunohistochemical features allows reliable separation.

Keywords: Melanocytic, naevi, perineurial, desmoplastic, neurotisation.

Introduction

Neurotisation is a well-established phenomenon in melanocytic naevi [1-3]. It is characterised by spindle cell morphology of dermal melanocytes showing Schwann cell and Meissnerian differentiation. In its extreme form neurotised naevi closely resemble a neurofibroma [1-3]. EMA expression is distinctly unusual in melanocytic naevi [4, 5]. It has rarely been described in congenital and acquired naevi with prominent spindle cell differentiation [6, 7]. Perineurial differentiation was reported in two acquired naevi with spindle cell differentiation (so called "perineuriomatous melanocytic naevi") [8]. These tumours show distinctive morphological features in addition to EMA expression as evidence of their perineurial differentiation. They are poorly studied but may be mistaken for desmoplastic melanoma [8]. We now aim to

further characterise the clinico-pathological features of this unique group of melanocytic tumours and provide helpful clues to allow separation from desmoplastic melanoma.

Material and methods

Between 2013 and 2017, six melanocytic naevi showing prominent spindle cell differentiation and EMA expression of the dermal component were encountered in the routine and referral practice of one of the authors (TB). Routine haematoxylin and eosin stained sections were reviewed and immunohistochemical studies were performed following standard protocols. The antibodies used, their dilutions and sources are provided in Table 1. Clinical follow-up was obtained from patient records.

Results

Clinical data

All patients were adults with a median and mean age of 48 years (range: 26-74) and a male to female ratio of 2:1. The anatomic distribution was wide and included the trunk (abdomen and shoulder), the extremities (arm and thigh), the neck and the scalp. The clinical presentation was of a longstanding naevus, an atypical naevus or a firm papule. Recent change was noted in two cases and one patient had a personal history of a thin superficial spreading melanoma on the opposite leg. The submitting diagnosis of the five referred cases was desmoplastic melanoma in three and neurotised naevus with perineurial differentiation in two cases. The clinical findings are summarized in Table 2.

Follow-up

Follow-up ranged from 6 to 48 months (median: 13, mean: 18). All patients were alive with no evidence of disease. Four tumours were completely removed at time of biopsy. Two tumours were initially partially sampled. One of these was treated by subsequent complete excision. There was no evidence of recurrence or metastasis. One patient was treated for a presumed diagnosis of desmoplastic melanoma. He had a negative re-excision and a negative axillary sentinel lymph node biopsy.

Histological features

All tumours were dermal based, well-circumscribed but asymmetrical (Fig. 1a and b). Three tumours showed additional extension into underlying adipose tissue (Fig. 1b). The measured tumour thickness ranged from 3 mm to 10 mm (median: 4.8). A biphasic growth pattern was evident and a pre-existing lentiginous compound naevus was present at least focally in the superficial aspect in all cases (Fig. 1c). The junctional component was lentiginous in two and lentiginous and nested in four cases. There was architectural atypia in one case but there was no cytological atypia or Pagetoid spread and no significant shoulder formation was observed. The associated naevic dermal component was located in superficial dermis. It was composed of bland ovoid to epithelioid melanocytes and showed no cytological atypia or mitotic activity (Fig. 1c). There was an abrupt transition to a more deeply seated larger spindle cell proliferation with well-circumscribed nodular outlines and a dumbbell shaped appearance in one case. This part comprised most of the dermal component and was composed of bland and uniform spindle cells arranged in short fascicles and embedded in a variably loose fibrous or myxoid stroma (Fig. 1d). In areas, the spindle cells showed slender wavy nuclei with a whorled growth pattern (Fig. 1e). The spindle cells showed no cytological

atypia or mitotic activity. An additional finding was the presence of distinctive intralesional hypocellular fibrous nodules and bands, and in the periphery of the tumour scattered lymphoid aggregates were present (Fig. 1f).

Immunohistochemistry

S100 expression was seen in the junctional part and throughout the dermal components including the spindle cell area (Fig. 2a and b). Melan A was expressed in melanocytes of the junctional and dermal naevic compartments. Scattered spindle cells also showed melan A expression (Fig. 2c). In contrast, HMB-45 staining was confined to the junctional component. EMA expression was present in a subset of the dermal spindle cells highlighting the long bipolar cytoplasmic processes (Fig. 2d). These cells also expressed Glut-1 and less prominently claudin-1 (Fig. 2e and f). Double labelling with antibodies against S100 and EMA demonstrated that the EMA and S100 were expressed in distinct cellular subpopulations which appeared intimately associated (Fig. 3a and b). The Ki67 proliferative index was low.

Discussion

We report a group of benign acquired naevi with distinctive and reproducible histological features characterised by prominent spindle cell morphology and perineurial differentiation of the dermal component. These tumours appear to be genuinely rare. Only two such tumours are documented in the literature and the majority of cases in this study were encountered in the referral rather than routine diagnostic setting. Clinically, these naevi affect middle aged adults with a male predilection. They present as papules with a wide anatomical distribution and a predilection for areas with intermittent rather than chronic sun exposure. A longstanding history and recent change are frequent findings. The

characteristic unifying histological features are the presence of a benign lentiginous compound naevus in the superficial aspect and a larger nodular spindle cell component in the deeper reaches. The spindle cells are bland and uniform, and in areas they show long biphasic cytoplasmic processes and wavy nuclei characteristic of perineurial cells. They are embedded in a loose fibromyxoid stroma with admixed distinctive hypocellular fibrous nodules and scattered peripheral lymphoid aggregates.

The spindle cell differentiation observed in these naevi likely reflects extensive neurotisation in a longstanding naevus [6, 8]. Neurotisation is not an infrequently encountered phenomenon, often seen in naevi of the head and neck area [3]. Neurotised naevi are characterised by spindle cell differentiation of dermal melanocytes (so-called "type C melanocytes"). The melanocytes resemble Schwann cells, and Meissnerian differentiation may also be seen. In the more developed stages the appearances closely resemble a neurofibroma with loosely arranged spindled melanocytes in a fibromyxoid matrix. A subset of neurotised naevi show a prominent desmoplastic or sclerotic stromal reaction, so called 'desmoplastic naevi' [9-13]. The spindle cells retain S100 expression by immunohistochemistry. At least scattered melan A expression and the presence of a background of a conventional naevus at least focally are clues to the diagnosis. Perineurial differentiation is characterised by the presence of slender spindle cells with wavy nuclei and elongated bipolar cytoplasmic processes in a whorled arrangement as seen in perineurioma [14-18]. Immunohistochemically, perineurial cells express EMA, Glut-1 and claudin-1 but they are negative for S100 [14-16, 18]. While claudin-1 expression has been reported also in a significant subset of melanocytic naevi and melanoma, EMA expression is distinctly rare [5, 6, 19-21]. It appears to represent an unusual form of neurotisation observed in a small subgroup of neurotised naevi only [6-8]. The

dermal component of these tumours is composed predominantly of S100-positive spindled melanocytes and in areas, spindle cells with perineurial differentiation are closely admixed. The perineurial cells are characterized by EMA staining with co-expression of the other perineurial markers, claudin-1 and Glut-1. They are negative for S100 and form a distinct cellular compartment as appreciated on double labelling for S100 and EMA. The findings are analogous to those observed in hybrid schwannoma-perineurioma [22].

The importance of describing this finding as a distinct entity is to increase awareness due to the resemblance with desmoplastic melanoma to spare the patient further extensive surgery and the psychological and social impact of a diagnosis of melanoma. This pitfall is reflected by the fact that there was a high index of suspicion for desmoplastic melanoma for the cases referred for a second opinion. In contrast to the naevi with perineurial differentiation, desmoplastic melanoma is a tumour of chronically and severely sun-damaged skin with a predilection for the head and neck of the elderly [13, 23-27]. It typically presents as larger and often indurated plaques. Histologically, it shows a diffusely infiltrative growth within dermis and subcutis, often with additional invasion into underlying skeletal muscle and fascia. The spindled tumour cells show at least a degree of cytological atypia and they induce a sclerotic stromal response. Furthermore, desmoplastic melanoma rarely arises from a pre-existing benign lentiginous compound naevus and melan A expression is rare [12]. Increased Ki-67 staining in desmoplastic melanoma has been found helpful at least in the differentiation from other desmoplastic/sclerotic naevi [12, 13]. The presence of peripheral lymphoid aggregates is not a good distinguishing feature as it may be seen in both desmoplastic melanoma and naevi with perineurial differentiation. Similarly, the expression

of EMA is not unique to naevi with perineurial differentiation and has rarely been documented in desmoplastic melanoma [21].

The differential diagnosis also includes other melanocytic tumours with spindle cell differentiation such as heavily neurotised naevi and desmoplastic naevi [9-11]. The distinction is possible by demonstration of EMA expression but is of little clinical consequence in view of the benign behaviour of these tumours. Similarly, nerve sheath tumours enter the differential diagnosis. Neurofibroma, solitary circumscribed neuroma, perineurioma and hybrid schwannoma-perineurioma may resemble melanocytic naevi with perineurial differentiation. The main distinguishing factor is the presence of a more conventional compound naevus and at least focally retained melan A expression. Malignant peripheral nerve sheath tumour is exceptionally rare in the skin outside the clinical setting of neurofibromatosis-1. It is characterized by increased cellularity and more pronounced cytological atypia.

In conclusion, we outline the clinical, histological and immunohistochemical characteristics of a distinct group of benign melanocytic naevi showing perineurial differentiation. Although these tumours show some overlapping histological features with desmoplastic melanoma, separation is possible using the constellation of clinical setting, histological clues and immunohistochemical phenotype. Awareness and recognition of these rare benign melanocytic tumours is important to avoid misdiagnosis as desmoplastic melanoma with implication for over treatment.

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Figure legends

Figure 1: The tumours are dermal based and relatively well-circumscribed. They have a biphasic appearance with a pre-existing conventional naevus in the superficial aspect and a spindle cell proliferation in the deeper reaches of the dermis. Also note the peripheral lymphoid aggregate (a). Extension into superficial subcutaneous adipose tissue may be seen. Also note the circumscription of the dumbbell-shaped dermal component (b). There is an abrupt transition of a conventional lentiginous compound naevus to the more deeply seated dermal spindle cell proliferation (c). The deeper dermal component is composed of bland and uniform spindle cells arranged in short bundles in a loose fibromyxoid stroma (d). In other areas, the tumour shows a whorled arrangement of spindle cells in a sclerotic fibrous stroma. There is no cytological atypia or mitotic activity (e). The presence of admixed intradermal hypocellular nodules and bands was a characteristic feature in all tumours (f).

Figure 2: By immunohistochemistry, S100 is expressed strongly and diffusely throughout the tumour (a). In the deeper spindle cell component expression of S100 is retained (b) and there is scattered melan A staining (c). Perineurial differentiation is identified in dermal spindle cells by immunohistochemical staining for EMA (d), glut-1 (e) and claudin-1 (f).

Figure 3: Double labelling for S100 (red) and EMA (brown) shows strong EMA expression in the deeper aspects of the tumour (a) and highlights that S100 and EMA expression is seen in different cellular compartments (b).

Table 1. Immunohistochemistry (antibodies, dilution and sources)

Antibody	Dilution	Sources
Claudin-1	1:50	Zymed, So. San Francisco, CA
EMA	1:800	Dako UK Ltd, Cambridge, UK
GLUT1	1:1500	Epitomics, Burlingame, CA
Ki67 (Mib-1)	1:100	Dako UK Ltd, Cambridge, UK
Melan-A (A103)	1:75	Dako UK Ltd, Cambridge, UK
S100	1:1500	Dako UK Ltd, Cambridge, UK

Table 2. Clinical data and follow-up

Case	Age	Sex	Location	F/U	F/U period (months)
1	36	M	scalp	ANED	6
2	74	F	arm	ANED	6
3	48	M	thigh	ANED	18
4	55	M	abdomen	ANED	8
5	47	F	shoulder	ANED	24
6	26	M	neck	ANED	48

ANED : alive with no evidence of disease ; F/U : follow-up